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(54) Title: RIBAVIRIN–PEGYLATED INTERFERON ALFA INDUCTION HCV COMBINATION THERAPY

(57) Abstract

The use of ribavirin and interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatitis C infection, e.g., a patient having HCV genotype 1, 2 or 3, to eradicate detectable HCV–RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period of at least 20 to 30 wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon–alfa, e.g., pegylated interferon–alfa–2b sufficient to at least substantially lower, and preferably to eradicate, detectable HCV–RNA, are administered; and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon–alfa are administered sufficient to maintian no detectable HCV–RNA for at least 20–30 weeks are administered after the end of the first treatment time period and to maintain no detectable HCV–RNA for at least 24 weeks after the end of the second treatment time period is disclosed.

RIBAVIRIN-PEGYLATED INTERFERON ALFA INDUCTION HCV COMBINATION THERAPY
BACKGROUND OF THE INVENTION

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The present invention relates to the use of ribavirin, pegylated interferon alfa and compbinations thereof for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised by administering a therapeutically effective induction amount of ribavirin and a therapeutically effective induction amount of pegylated interferon-alfa for a first treatment time period sufficient to substantially lower detectable HCV-RNA, followed by (2) administering a therapeutically effective amount of ribavirin and an therapeutically effective amount of pegylated interferon-alfa for a second treatment time period sufficient to eradicate detectable HCV-RNA at least by the end of the second treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

Chronic infection with hepatitis C virus is an insidious and slow-progressing disease having a significant impact on the quality of life. It can eventually result in cirrhosis of the liver, decompensated liver disease and/or hepatocelluar carcinoma.

International Publication No. WO98/48840 discloses use of pegylated interferon alfa to treat hepatitis C infections.

Nieforth et al. (Clin. Pharmacol. Ther., 1996, 59:636-646) has reported a comparison of the in vivo activity of Roferon®A and a polyethylene glycol-modified Roferon®A in healthy volunteers. The

results, however, suggested that the conjugates could not be administered less than twice weekly and therefore offered little therapeutic advantage over the unmodified counterpart.

5   Co-pending, commonly assigned U.S. Patent Application Serial No. 08/742,305 discloses methods of administering polymer-cytokine conjugates to individuals susceptible to treatment with the cytokine, but does not disclose the method of this invention.

10   Polyethylene glycol modification of other proteins has been reported by Fuertges et al. (Journal of Controlled Release,**1990**, Vol.11:139-48).

        Combination therapy of interferon alfa-2b and ribavirin to treat
15   chronic hepatitis C for 24 weeks is disclosed by Reichard et al. (Lancet 1998; 351;83-87)

        T. Poynard et al. (Lancet, **1998**, Vol. 352, 1426-1432) disclose that treating chronic hepatitis C patients who had not been treated with
20   interferon or ribavirin with 3 MIU of interferon alfa-2b TIW plus 1000-1200 mg of ribavirin per day for 48 weeks resulted in a sustained virological response at 24 weeks after treatment in 43% of the patients. See also J. G. McHutchinson et al. (N. Engl. J. Med., 1998, 339:1485-1492), G. L. Davis et al. (N. Engl. J. Med. 339:1493-1499) disclose that treating
25   chronic hepatitis C patients who relapsed after treatment with interferon with 3 MIU of interferon alfa 2b Tim plus 100-1200 mg of ribavirin per day for 48 weeks results in higher rates of sustained virologic response than treatment with interferon alone.

30   There is a need to provide an improved therapy for treating chronic hepatitis C patients to produce a sustained virological response at 24 weeks after treatmen in agreater number of patients.

SUMMARY OF THE INVENTION

The present invention provides the use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having

5   chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods:(a) a first treatment time period,

10   wherein a therapeutically effective amount of ribavirin and an therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to sustantially lower detectable HCV-RNA serum levels, and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective

15   amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to eradicate detectable HCV-RNA at least 20 to 30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

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The present invention also provides the use of pegylated interferon alpha for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of

25   pegylated interferon alpha in association with an effective amount of ribavirin characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period,wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-

30   alfa are administered for a time period sufficient to sustantially lower detectable HCV-RNA serum levels, and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to eradicate detectable HCV-

3

RNA at least 20 to 30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

5   The present invention also provides the use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of

10   pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to

15   sustantially lower detectable HCV-RNA serum levels, and by (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to eradicate detectable HCV-RNA at least 20 to 30 weeks after the end of the first

20   treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

       The present invention also provides the use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having

25   chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period,

30   wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to eradicate detectable HCV-RNA, and (b) a second treatment time period of at least 20 to 30

4

weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintain no detectable HCV-RNA for at least 20-30 weeks after the end of the first treatment time period and to maintain

5   no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

       The present invention also provides the use of pegylated interferon alpha for the manufacture of a pharmaceutical composition for treating a

10   patient having chronic hepatitis C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of pegylated interferon alpha in association with an effective amount of ribavirin characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment

15   time period, wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to eradicate detectable HCV-RNA, and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a

20   therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintain no detectable HCV-RNA for at least 20-30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

25

       The present invention also provides the use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an

30   effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of

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ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to eradicate detectable HCV-RNA, and (b) a second treatment time period of at least 20 to 30 weeks a therapeutically effective amount of ribavirin and

5   a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to maintain no detectable HCV-RNA for at least 20-30 weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

10

The present invention also provides the use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an

15   effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (1) a first treatment time period of about at least about four weeks, wherein about 400-1200 mg per day, preferably about 800-1200 mg per day, of

20   ribavirin and about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b twice a week are administered, (2) a second treatment time period of about up to about forty-four weeks, wherein about 800-1200 mg per day of ribavirin and about 1.0 to 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week are administered.

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The present invention also provides the use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an

30   effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (1) a first treatment time period of about at least about four up to about twelve

6

weeks, wherein about 400-1200 mg per day, preferably about 800-1200

mg per day, of ribavirin and about 1.5 micrograms per kilogram of

pegylated interferon-alfa-2b twice a week are administered, (2) a second

treatment time period of about thirty-six up to about forty-four weeks,

5   wherein about 800-1200 mg per day of ribavirin and about 0.5 to 1.5

micrograms per kilogram once a week, preferably about 1.0 to 1.5

micrograms per kilogram of pegylated interferon-alfa-2b once a week are

administered.

10   **DETAILED DESCRIPTION**

The present method of treating patients having chronic hepatitis C

infections comprises two treatment time periods. In the first treatment time

period, a therapeutically effective induction dosing amount of ribavirin and

15   an therapeutically effective induction dosing amount of pegylated

interferon-alfa is administered for a first treatment time period sufficient to

substantially lower detectable HCV-RNA serum levels, preferably by a

power of 10, more preferrably by at least two powers of ten, i.e., at least

10^2 , lower than the initial HCV-RNA serum level. In a preferred

20   embodiment of the present invention, the HCV-RNA is eradicated

(i.e.,lowered to less than 100 copies/mL) during the first treatment time

period. In the second treatment time period, the method entails

administering a therapeutically effective amount of ribavirin and an

therapeutically effective amount of pegylated interferon-alfa long enough

25   to eradicate detectable HCV-RNA at least by the end of the second

treatment time period and to maintain no detectable HCV-RNA for at least

24 weeks after the end of the second treatment time period. In a

preferred embodiment of the present invention , the HCV-RNA is

eradicated (i.e., lowered to less than 100 copies/mL) during the second

30   treatment time period and more preferably by the end of the first treatment

time period; in this preferred embodiment the no detectable HCV-RNA

level is maintained during the second treatment time period. The sum of

the first and second treatment time periods is about 40-50 weeks preferrably 48 weeks.

5   The amount of ribavirin administered in the first treatment time period is from 400 to 1600 mg per day, preferrably 600 to 1200 mg/day or about 800 to 1200 mg day and most preferably about 1000 to 1200 mg/kg a day. The amount of ribavirin administered in the second treatment time period is in the range of from about 800 to 1200 mg per day, preferably from about 1000 to 1200 mg per day.

10

The following preferred embodiments for administering pegylated interferon alfa are presented.

When the pegylated interferon-alfa administered is a
15   pegylated interferon alfa-2b, the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram twice a week (BIW) for at least four up to twelve weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is in the range of 0.5 to
20   1.5 micrograms per kilogram once a week (QW) for thirty-six up to to forty-four weeks.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the induction dosing amount of pegylated interferon
25   alfa-2b administered in first treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram twice a week (BIW) for twelve weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram once a week (QW) for thirty-six weeks.

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When the pegylated interferon-alfa administered is a pegylated interferon alfa-2b, the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period of five weeks is in the

8

range of 0.5 to 1.5 micrograms per kilogram BIW (preferably

1.5microgram per kilograms BIW) for one week, followed by 0.5 to 1.0

micrograms per kilogram BIW (preferably 1.0 micrograms per kilogram

BIW) for four weeks, and the amount of pegylated interferon alfa-2b

5   administered in the second treatment time period of forty-three weeks is in

the range of 0.5 to 1.5 micrograms per kilogram once a week, prefrably

0.5 to 1.0 micrograms per kilogram once a week.

When the pegylated interferon-alfa administered is a pegylated

10   interferon alfa-2b, the induction dosing amount of pegylated interferon

alfa-2b administered in first treatment time period is in the range of 1.5

microgram per kilogram BIW for four weeks, and the amount of pegylated

interferon alfa-2b administered in the second treatment time period is in

the range of 0.5 micrograms per kilogram once a week for to forty-four

15   weeks.

When the pegylated interferon-alfa administered is a pegylated

interferon alfa-2b, the induction dosing amount of pegylated interferon

alfa-2b administered in first treatment time period of five weeks is in the

20   range of 1.5 micrograms per kilogram BIW for one week, followed by 1.0

micrograms per kilogram BIW for four weeks, and the amount of

pegylated interferon alfa-2b administered in the second treatment time

period of thirty-six to forty-four weeks is in the range of 0.5 to 1.0

micrograms per kilogram once a week.

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When the pegylated interferon-alfa administered is a pegylated

interferon alfa-2b, the induction dosing amount of pegylated interferon

alfa-2b administered in first treatment time period is 1.5 micrograms per

kilogram BIW for twelve weeks, and the amount of pegylated interferon

30   alfa-2b administered in the second treatment time period is in the range

1.0 micrograms per kilogram once a week for thirty-six weeks.

When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the induction dosing amount of pegylated interferon alfa-2a administered in first treatment time period is in the range of 20 to 250 micrograms BIW, preferably 90 to 180 micrograms BIW, for at least

5   four weeks, and the amount of pegylated interferon alfa-2a administered in the second treatment time period is in the range of 20 to 250 micrograms once a week(QW), preferably 90 to 180 micrograms QW, for up to forty-four weeks.

10   When the pegylated interferon-alfa administered is a pegylated interferon alfa-2a, the induction dosing amount of pegylated interferon alfa-2a administered in first treatment time period is in the range of 20 to 250 micrograms BIW, preferably 90 to 180 micrograms BIW, for four to twelve weeks, and the amount of pegylated interferon alfa-2a

15   administered in the second treatment time period is in the range of 20 to 250 micrograms once a week, preferably 90 to 180 micrograms QW, for thirty-six to forty-four weeks.

When the pegylated interferon-alfa administered is a pegylated

20   interferon alfa-2a, the induction dosing amount of pegylated interferon alfa-2a administered in first treatment time period is in the range of 20 to 250 micrograms BIW for one week, preferably 90 to 180 micrograms BIW for one week, followed by 20 to 200 micrograms BIW for four weeks, preferably 90 to 180 micrograms BIW for four weeks and the amount of

25   pegylated interferon alfa-2a administered in the second treatment time period is in the range of 20 to 250 micrograms once a week(QW), preferably 90 to 180 micrograms QW for forty-three weeks.

When the pegylated interferon-alfa administered is a pegylated

30   interferon alfa-2a, in first treatment time period, the induction dosing amount of pegylated interferon alfa-2a administered is in the range of 20 to 250 micrograms BIW, preferably 90 to 180 micrograms BIW, for twelve weeks, and the amount of pegylated interferon alfa-2a administered in the

second treatment time period is in the range of 20 to 250 micrograms per week on a weekly basis(QW), preferably 90 to 180 micrograms QW, for thirty-six weeks.

5   The term "pegylated interferon alfa" as used herein means polyethylene glycol modified conjugates of interferon alfa, preferably interferon alfa-2a and -2b. The preferred polyethylene-glycol-interferon alfa -2b conjugate is PEG$_{12000}$-interferon alfa 2b. The phrases "12,000 molecular weight polyethylene glycol conjugated interferon alpha" and

10   "PEG$_{12000}$-IFN alfa" as used herein mean conjugates such as are prepared acording to the methods of International Application No. WO 95/13090 and containing urethane linkages between the interferon alfa-2a or -2b amino groups and polyethylene glycol having an average molecular weight of 12000.

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          The preferred PEG$_{12000}$-interfferon alfa-2b is prepared by attaching a PEG polymer to the epsilon amino group of a lysine residue in the IFN alfa-2b molecule. A single PEG$_{12000}$ molecule is conjugated to free amino groups on an IFN alfa-2b molecule via a urethane linkage. This conjugate

20   is characterized by the molecular weight of PEG$_{12000}$ attached. The PEG12000-IFN alfa-2b conjugate is formulated as a lyophilized powder for injection. The objective of conjugation of IFN alfa with PEG is to improve the delivery of the protein by significantly prolonging its plasma half-life, and thereby provide protracted activity of IFN alfa.

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          The term " interferon-alfa " as used herein means the family of highly homologous species-specific proteins that inhibit viral replication and cellular proliferation and modulate immune response. Typical suitable interferon-alfas include, but are not limited to, recombinant interferon alfa-

30   2b such as Intron-A interferon available from Schering Corporation, Kenilworth, N.J., recombinant interferon alfa-2a such as Roferon interferon available from Hoffmann-La Roche, Nutley, N.J., recombinant interferon alpha-2C such as Berofor alpha 2 interferon available from Boehringer

Ingelheim Pharmaceutical, Inc., Ridgefield, CT., interferon alpha-n1, a purified blend of natural alfa interferons such as Sumiferon available from Sumitomo, Japan or as Wellferon interferon alpha-n1 (INS) available from the Glaxo-Wellcome Ltd., London, Great Britain, or a consensus alpha

5   interferon such as those described in U.S. Patent Nos. 4,897,471 and 4,695,623 (especially Examples 7, 8 or 9 thereof) and the specific product available from Amgen, Inc., Newbury Park, CA, or interferon alfa-n3 a mixture of natural alfa interferons made by Interferon Sciences and available from the Purdue Frederick Co., Norwalk, CT., under the Alferon

10   Tradename. The use of interferon alfa-2a or alpha 2b is preferred. Since interferon alpha 2b, among all interferons, has the broadest approval throughout the world for treating chronic hepatitis C infection, it is most preferred. The manufacture of interferon alpha 2b is described in U.S. Patent No. 4,530,901.

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Other interferon alfa conjugates can be prepared by coupling an interferon alfa to a water-soluble polymer. A non-limiting list of such polymers include other polyalkylene oxide homopolymers such as polypropylene glycols, polyoxyethylenated polyols, copolymers thereof

20   and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinylpyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon alfa-polymer conjugates are described in U.S. Patent No. 4,766,106, U.S. Patent No.

25   4,917,888, European Patent Application No. 0 236 987, European Patent Application No. 0510 356 0 593 868 and 0 809 996 (pegylated interferon alfa-2a) and International Publication No. WO 95/13090.

Pharmaceutical composition of pegylated interferon alfa-suitable for

30   parenteral administration may be formulated with a suitable buffer, e.g., Tris-HCl, acetate or phosphate such as dibasic sodium phosphate/monobasic sodium phosphate buffer, and pharmaceutically acceptable excipients (e.g., sucrose), carriers (e.g. human serum

12

albumin), toxicity agents (e.g. NaCl), preservatives (e.g. thimerosol, cresol or benylalcohol), and surfactants(e.g. tween or polysorabates) in sterile water for injection. The pegylated interferon alfa-may be stored as lyophilized powders under a refrigeration at 2°-8°C. The reconstituted

5   aqueous solutions are stable when stored between 2° and 8°C and used within 24 hours of reconstitution. See for example U.S. Patent Nos, 4,492,537; 5,762,923 and 5,766,582.

The term "patients having chronic hepatitis C infections" as used

10   herein means any patient having chronic hepatitis C and includes treatment naive patients, relapsers and non-responders.

These patients having chronic hepatitis C include those who are infected with mutiple HCV genotypes including type 1 as well as those

15   infected with,*inter alia*, HCV genotypes 2 2 and/or 3 as well as HCV genotypes 2, 3, 4, 5 and/or 6 and other possible HCV genotypes.

The term "treatment naive patients" as used herein means patients with chronic hepatitis C who have never been treated with ribavirin or any

20   interferon, including but not limited to interferon-alfa, or pegylated interferon alfa.

The term "relapsers" as used herein means patients with chronic hepatitis C who have relapsed after initial response to previous treatment

25   with interferon alone, or in combination with ribavirin.

The term "non-responders" as used herein means patients with chronic hepatitis C who have not responded to prior treatment with any interferon alone, or in combination with ribavirin.

30

A person suffering from chronic hepatitis C infection may exhibit one or more of the following signs or symptoms:

(a) elevated ALT,

(b) positive test for anti-HCV antibodies,

5   (c) presence of HCV as demonstrated by a positive test for   the
presence of HCV-RNA in the serum,

(d) clinical stigmata of chronic liver disease,

10   (e) hepatocelluar damage.

To practice the invention, the combination therapy of pegylated
interferon-alfa and ribavirin is administered to the patient exhibiting one of
more of the above signs or symptoms in the first and second treatment
15   time periods in amounts sufficient to eliminate or at least alleviate one or
more of the signs or symptoms.

Ribavirin is administered to the patient in association with pegylated
interferon-alfa, that is, the pegylated interferon-alfa dose is administered
20   during the same period of time that the patient receives doses of ribavirin.
Pegylated interferon-alfa formulations are not effective when administered
orally, so the preferred method of administering the pegylated interferon-
alfa is parenterally, preferably by subcutaneous, IV, or IM, injection.
Ribavirin may be administered orally in capsule or tablet form in
25   association with the parenteral administration of pegylated interferon-alfa .
Of course, other types of administration of both medicaments, as they
become available are contemplated, such as by nasal spray,
transdermally, by suppository, by sustained release dosage form, and by
pulmonary inhalation. Any form of administration will work so long as the
30   proper dosages are delivered without destroying the active ingredient.

The term "no detectable HCV-RNA" in the context of the present
invention means that there are fewer than 100 copies of HCV-RNA per ml

14

of serum of the patient as measured by quantitative, multi-cycle reverse
transcriptase PCR methodology. HCV-RNA is preferably measured in the
present invention by the methodology described below. This methodology
is referred to herein as HCV-RNA/qPCR. The lower limit of detection of
5   HCV-RNA is100 copies/mL

RNA is extracted from patient serum using a guaninidium
thiocyanate- phenol-chloroform mister followed by ethanol-ammonium
acetate precipitation. The precipitated RNA is centrifuged and the
10   resulting pellet is dried in a Centrivap console (Labconco, Kansas City,
Mo.). The dry pellet is then resuspended in 30 microliters of an Rnasin
(Promega Corp., Madison, WI), dithiothritol, and diethylpyrocarbonate-
treated water mixture. Samples are kept at or below -20°C (preferably
below -70°C) until RNA reverse transcription (RT) and PCR.
15

In order to convert the entire RNA sequence into cDNA in the RT
reaction, random hexadeoxyribonucleotides (Pharmacia Biotech,
Piscataway, NJ) are used as primers for the first strand cDNA synthesis.
Two aliquots of 3 microliters of resuspended sample are added to 3
20   microliters of 100ng/μl random primers and denaturated at 70°C, then
reverse transcribed at 40°C for one hour using M-MLV reverse
transcriptase (USB, Cleveland, OH) in standard buffer containing 5 mM
$MgCl_2$. The final RT reaction volume is 26 μl. The PCR is started
immediately following the reverse transcription.
25

A modified version of the PCR method is performed using heat-
stable Taq polymerase to amplify the cDNA. Seventy-five microliters of
PCR mix is added to the entire RT reaction volume (26 μl) to a final $MgCl_2$
concentration of 1.5 mM in a total volume of 101 μl. Each 101 μl sample
30   is then split into 50.5 μl, and a layer of mineral oil is placed on top to
prevent evaporation.

The PCR cycle consists of annealing for 90 sec., extension for 90
sec., and denaturation for 90 sec., at 55°C, 74°C and 94°C, respectively.
Thermocycling samples is submitted to a final 74°C extension for 10
minutes. Four different cycle sets are used. By loading the sample in

5   duplicate, and splitting these samples evenly after RT, there are four
tubes from one sample. Each of the four tubes is given a different cycle
number, enhancing sensitivity and accuracy in the quantitation process.
The thermocycling efficiency will be assessed by satisfactory amplification
of known copy number RNA standards included in each set of 60 tubes.

10   Two primer sets are used for the amplification, both from the 5'
untranslated region of the HCV genome. Both of these primer sets are
highly conserved and detect all known subtypes of HCV. Primer set 1:
upstream 5' -GTG GTC TGC GGA ACC GGT GAG T-3', downstream 5'-
TGC ACG GTC TAC GAG ACC TC-3' which produces a 190 bp product.

15   Primer set 2: upstream 5'-CTG TGA GGA ACT ACT GTC TTC-3',
downstream 5'-CCC TAT CAG GCA GTA CCA CAA-3' which produces a
256 bp product.

The amplified cDNA is then electrophorised in 3% agarose gel and

20   transferred to nylon membrane. The target DNA is detected by Southern
blotting and immunostaining using a nonradioactive digoxigenin-labeled
DNA probe. These procedures are performed using automated
instruments for PCR thermocycling, agarose gel electrophoresis, vacuum-
transfer Southern blot, hybridization, and immunostaining. Each

25   membrane contains known copy number serially diluted standards which
are used to construct standard curves for quantitative measurement of the
specimen bands. Originally standard curves are made from carefully
diluted HCV-RNA from transcribed clones. Radioactive incorporation
studies, gel electrophoresis, and OD 260 are performed on the transcripts

30   to determine that they are of the expected length. After the production of
the RNA transcripts quantitated clone standards "pooled" standards are
generated which better represent the heterogeneous nature of HCV, one
would encounter in natural infection. These pools are made by combining

large amounts of serum or plasma from known infected individuals. The serum/plasma pools are calibrated with PCR, against the clone transcripts and then diluted in the known PCR-negative fluids. Finally, the higher copy number samples of the pools are checked against the cDNA

5   Quantiplex nucleic acid detection system from Chiron Inc. (Emeryville, CA). These "double quantitated" pools are aliquoted and saved at -70°C. Dilutions of 5,000,000, 1,000,000, 500,000, 100,000, 10,000, and 1000 copies/ml are used in each experiment.

10   Each Southern blot membrane is scanned into a computer using an automated scanner/densitometer, at intervals during development to determine when the standard curve is most linear. The resultant electronic images are then measured for band area and mean band density. All of the reading are standardized to integrated band density

15   and compared to the standard curve to obtain a numerical value of viral copy number for each band.

         The term "sustained virologic response" as used in the context of the present invention means that there is no detectable HCV-RNA in the

20   patients treated in accordance with the present invention for at least 24 weeks after the end of the combined therapy treatment. Preferably, the period of sustained virologic response will be at least one year - or longer - after the end of treatment. For HCV genotyping, INNO-L PA HCV (Innogenetics, Zeijmaurde, Belgium) second generation assay may be

25   used.

         The following clinical protocol may be used to administer the combination therapy of the present invention:

30   Overall Design and Plan of the Study

         A prospective, multicenter, randomized, double-blind, parallel-group will be used. Two studies each with two treatment regimes will be used. Study No. 1 will compare treatment with pegylated Intron A, 1.5

17

micrograms per kilogram SC once a week (QW) in combination with
ribavirin,1000 to 1200 mg per day PO for four weeks followed by
pegylated Intron A, 0.5 micrograms per kilogram SC once a week, in
combination with ribavirin, 1000 to 1200 mg per day PO for forty-four

5   weeks to treatment with pegylated Intron A, 1.5 micrograms per kilogram
SC once a week in combination with ribavirin, 1000 to 1200 mg per day
PO for forty-eight weeks. Study No. 2 will compare treatment of pegylated
Intron A, 1.5 micrograms per kilogram SC BIW in combination with
ribavirin, 1000-1200 mg/day PO for four weeks followed by pegylated

10   INTRON A 1.5 micrograms/kilogram SC QW in combination with ribavirin,
1000-1200 mg/day PO for forty-four weeks to the treatment REBETRON
Combination Therapy (Intron A, 3 MIU SC TIW in combination with
ribavirin, 1000 to 1200 mg per day PO) for forty-eight weeks in patients
with compensated chronic hepatitis C. Eligible patients are those 18-65

15   years of age, male and female subjects who should have chronic hepatitis
C confirmed by positive serum HCV-RNA, liver biopsy, and laboratory
tests.

       Treatment group assignments should be made by a Central
20   Randomization Center. The randomization procedure should be designed
to attempt to balance the treatment groups, within and across sites, with
respect to presence or absence of cirrhosis in the pretreatment liver
biopsy, serum HCV-RNA/qPCR level, and HCV genotype.

25   During treatment and posttreatment follow-up, biochemical (ALT),
virological (HCV-RNA), and histological (liver biopsy) examinations would
be used to assess the nature and duration of response to study treatment.
The primary efficacy variable will be the overall response defined as loss
of serum HCV-RNA/qPCR (<100 copies/mL) as measured at 24 weeks

30   following the end of therapy. In addition, a decrease in hepatic
inflammation, an improvement in posttreatment liver biopsy as measured by
the Knodell Histology Activity index (HAI) and normalization of ALT will
also be examined as a secondary efficacy endpoints. The safety of the
study treatments will be assessed by monitoring selected laboratory

35   parameters and by also recording and evaluating the occurrence of any
adverse events.

Treatment Regimens

There are two studies , each with two treatment regimens :

5

STUDY # 1

1. (a)Pegylated INTRON® A 1.5 micrograms per kilogram SC once a week (QW) plus ribavirin 1000-1200 mg/Kg/day PO in two divided doses for 4 weeks; followed by

10

   (b)Pegylated INTRON® A 0.5 micrograms per kilogram SC INTRON® A once a week (QW) plus ribavirin 1000-1200 mg/Kg/day PO in two divided doses for 44 weeks.

15

2. (a) Pegylated INTRON® A 1.5 micrograms per kilogram once a week (QW) plus ribavirin 1000-1200 mg/Kg/day PO in two divided doses for 44 weeks.

20

STUDY # 2

3 (a) Pegylated INTRON® A 1.5 micrograms per kilogram twice a week (BIW) plus ribavirin 1000-1200 mg/Kg/day PO in
25   two divided doses for 4 weeks; followed by
   (b)Pegylated INTRON® A 1.5 micrograms per kilogram INTRON® A once a week (QW) plus ribavirin 1000-1200 mg/Kg/day PO in two divided doses for 44 weeks.

30

4. (a) INTRON® A 3 MIU SC three times a week (TIW) plus ribavirin 1000-1200 mg/Kg/day PO in two divided doses for 48 weeks.

Studies No. 1 and 2 including treatments 1 and 2 and 3 and 4 should be
35   administered for 48 weeks.

Exclusion Criteria: Patients having chronic hepatitis C who should

be excluded from treatment in accordance with the present invention

include, *inter alia.*, women who are pregnant or nursing; those with

40   suspected hypersensitivity to pegylated interferon alfa or ribavirin; those

with normal ALT at screenin or entry visit, as well as those with any known

pre existing condition(e.g. pre existing psychiatric condition especially

severe depression or a history of severe psychiatric disorder) that in the

opinion of the attending clinician would interfere with the subject's participation in and completion of the protocol.

5   The randomization procedure may be designed to balance the groups with respect to the following Baseline characteristics:

• pretreatment liver histology (cirrhosis or no cirrhosis);

• serum HCV-RNA/qPCR status (HCV-RNA/qPCR ≤2,000,000 or HCV-RNA/qPCR >2,000,000 copies/mL); and

• HCV Genotype (1 or other). Patients with mixed genotypes (which include
10   Type 1) will be classified as Type 1 for purposes of balancing.

Efficacy

The primary efficacy objective will be the sustained virologic response rate defined as loss of (detectable) serum HCV-RNA/qPCR
15   measured at 24 weeks following the end of therapy to an undetectable level or to a level <100 copies/mL. The following secondary efficacy Endpoints will also be examined:

The secondary efficacy Endpoints:

• proportion of patients with normalization of ALT at 24 weeks of
20   follow-up;

• proportion of patients with improvement in biopsy (Categories I + II +III combined scores);

• change from Baseline in the biopsy scores (Categories I + II + III combined scores);

25

• response rates at Endpoint of treatment based on HCV-RNA/qPCR;

• proportion of patients with normalization of ALT at Endpoint of treatment.

• response rates at 24 weeks of follow-up based on HCV-RNA/qPCR.

5

Virology: Entry Status and Change from Entry

Serum HCV-RNA/qPCR testing and genotype testing will be

5   performed by a central laboratory. A positive HCV-RNA assay result will
be required at Baseline; only patients positive for HCV-RNA will be eligible
to participate. Repeat assays should be scheduled at Weeks 4, 12, 24, 36
and 48. All patients should have repeat assays scheduled for Follow-up
Weeks 12 and 24.

10   Response will be assessed as defined below:

A patient will be classified as a sustained responder at a given time point if
HCV-RNA/qPCR is negative (<100 copies per mL) at that time point.

A patient will be classified as a sustained responder if the patient is a

15   responder at 24 weeks of follow-up.

Note that patients who do not meet these criteria, including patients who
discontinued before the required HCV-RNA/qPCR evaluations are
obtained, will be classified as non-responders.

Based on both serum HCV-RNA/qPCR and change in liver histology as

20   evaluated by the Knodell HAI Inflammation Score. A patient will be
classified as an overall responder to treatment if he/she is a sustained
responder and his/her Post treatment Knodell HAI inflammation score
(sum of categories I+II+III) improved by 2 or more units relative to the
Pretreatment score.

25

Liver Histology

Liver biopsy will be required within the six months preceding patient

5   enrollment and at Follow-up Week 24 for all patients. Evaluation of the

biopsies will be performed by a single pathologist using the Knodell

Histology Activity Score. The central pathologist will be blinded with

respect to patient identification, treatment group, and the time the biopsy will

be obtained relative to treatment (Pre- or Posttreatment). Efficacy of study

10   treatments will be assessed by comparing the degree of inflammatory

activity observed at Baseline with that present at Follow-up Week 24.

The patient's weight and their baseline disease characteristics

(HCV genotype and initial viral load) for all patients will be measured

15   before the start of the study. HCV genotypes should be done on the

patient serum samples subjected to HCV-RNA/qPCR testing.

This enhancement of efficacy included all aspects of the

disease will result in:

20   • Sustained eradication of detectable HCV-RNA;

          • Improvement in hepatic inflammation;

          • Normalization of ALT;

          • Improvement in HQL.

We claim:

1.   The use of ribavirin for the manufacture of a pharmaceutical
composition for treating a patient having chronic hepatitis C infection to
5   eradicate detectable HCV-RNA by a method comprising administering an
effective amount of ribavirin in association with an effective amount of
pegylated interferon alpha, characterised in that treating patients having
chronic hepatitis C infections is effected in two treatment time periods:(a)
a first treatment time period, wherein a therapeutically effective amount of
10   ribavirin and an therapeutically effective induction dosing amount of
pegylated interferon-alfa are administered for a time period sufficient to
sustantially lower detectable HCV-RNA serum levels, and (b) a second
treatment time period of at least 20 to 30 weeks wherein a therapeutically
effective amount of ribavirin and a therapeutically effective amount of
15   pegylated interferon-alfa are administered sufficient to eradicate
detectable HCV-RNA at least 20 to 30 weeks after the end of the first
treatment time period and to maintain no detectable HCV-RNA for at least
24 weeks after the end of the second treatment time period.

20   2.   The use of pegylated interferon alpha for the manufacture of a
pharmaceutical composition for treating a patient having chronic hepatitis
C infection to eradicate detectable HCV-RNA by a method comprising
administering an effective amount of pegylated interferon alpha in
association with an effective amount of ribavirin characterised in that
25   treating patients having chronic hepatitis C infections is effected in two
treatment time periods: (a) a first treatment time period,wherein a
therapeutically effective amount of ribavirin and a therapeutically effective
induction dosing amount of pegylated interferon-alfa are administered for
a time period sufficient to sustantially lower detectable HCV-RNA serum
30   levels, and (b) a second treatment time period of at least 20 to 30 weeks
wherein a therapeutically effective amount of ribavirin and a
therapeutically effective amount of pegylated interferon-alfa are
administered sufficient to eradicate detectable HCV-RNA at least 20 to 30

weeks after the end of the first treatment time period and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

5   3.   The use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha

10   characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to sustantially lower

15   detectable HCV-RNA serum levels, and by (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of ribavirin and a therapeutically effective amount of pegylated interferon-alfa are administered sufficient to eradicate detectable HCV-RNA at least 20 to 30 weeks after the end of the first treatment time period

20   and to maintain no detectable HCV-RNA for at least 24 weeks after the end of the second treatment time period.

4.   The use of ribavirin for the manufacture of a pharmaceutical composition for treating a patient having chronic hepatitis C infection to

25   eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha, characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (a) a first treatment time period, wherein a therapeutically effective amount of

30   ribavirin and a therapeutically effective induction dosing amount of pegylated interferon-alfa are administered for a time period sufficient to eradicate detectable HCV-RNA, and (b) a second treatment time period of at least 20 to 30 weeks wherein a therapeutically effective amount of

ribavirin and a therapeutically effective amount of pegylated interferon-alfa
are administered sufficient to maintain no detectable HCV-RNA for at least
20-30 weeks after the end of the first treatment time period and to
maintain no detectable HCV-RNA for at least 24 weeks after the end of
5   the second treatment time period.

5.   The use of pegylated interferon alpha for the manufacture of a
pharmaceutical composition for treating a patient having chronic hepatitis
C infection to eradicate detectable HCV-RNA by a method comprising
administering an effective amount of pegylated interferon alpha in
10   association with an effective amount of ribavirin characterised in that
treating patients having chronic hepatitis C infections is effected in two
treatment time periods: (a) a first treatment time period, wherein a
therapeutically effective amount of ribavirin and a therapeutically effective
induction dosing amount of pegylated interferon-alfa are administered for
15   a time period sufficient to eradicate detectable HCV-RNA, and (b) a
second treatment time period of at least 20 to 30 weeks wherein a
therapeutically effective amount of ribavirin and a therapeutically effective
amount of pegylated interferon-alfa are administered sufficient to maintain
no detectable HCV-RNA for at least 20-30 weeks after the end of the first
20   treatment time period and to maintain no detectable HCV-RNA for at least
24 weeks after the end of the second treatment time period.

6.   The use of both ribavirin and pegylated interferon alpha for the
manufacture of pharmaceutical compositions for treating a patient having
25   chronic hepatits C infection to eradicate detectable HCV-RNA by a
method comprising administering an effective amount of ribavirin in
association with an effective amount of pegylated interferon alpha
characterised in that treating patients having chronic hepatitis C infections
is effected in two treatment time periods: (a) a first treatment time period,
30   wherein a therapeutically effective amount of ribavirin and a
therapeutically effective induction dosing amount of pegylated interferon-
alfa are administered for a time period sufficient to eradicate detectable
HCV-RNA, and (b) a second treatment time period of at least 20 to 30
weeks a therapeutically effective amount of ribavirin and a therapeutically
35   effective amount of pegylated interferon-alfa are administered sufficient to
maintain no detectable HCV-RNA for at least 20-30 weeks after the end of
the first treatment time period and to maintain no detectable HCV-RNA for
at least 24 weeks after the end of the second treatment time period.

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7.   The use of any preceding claim, wherein the amount of ribavirin administered in the first and second treatment time periods is from 400 to 1600 mg per day, and preferably is from 600 to 1600 mg per day, or is

5   800 to 1200 mg per day, and more preferably is from 1000 to 1200 mg per day.

8.   The use of any preceding claim, wherein the pegylated interferon-alfa administered is pegylated interferon alfa-2a,or pegylated interferon

10   alfa-2b.

9.   The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the induction dosing amount of pegylated interferon alfa-2b administered in

15   first treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram BIW for at least four weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram per week on a weekly basis for up to forty-four weeks.

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10.   The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is in the range of 0.5 to 1.5 microgram per

25   /kilogram BIW for four to twelve weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is in the range of 0.5 to 1.5 micrograms per kilogram per week on a weekly basis for thirty-six to forty-four weeks.

30   11.   The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period of five weeks is in the range of 0.5 to1.5 micrograms per kilogram BIW for one week, followed by 0.5 to 1.0

35   micrograms per kilogram BIW for four weeks, and the amount of

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pegylated interferon alfa-2b administered in the second treatment time period of forty-three weeks is in the range of 0.5 to 1.5 micrograms per kilogram per week on a weekly basis.

5   12.   The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2b and wherein, the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is in the range of 0.5 to 1.5 micrograms/kilogram BIW for twelve weeks, and the amount of pegylated

10   interferon alfa-2b administered in the second treatment time period is in the range of 0.5 to 1.5 micrograms/kilogram per week on a weekly basis for thirty six weeks.

13.   The use of any preceding claim, wherein the pegylated interferon-

15   alfa administered is a pegylated interferon alfa-2b and wherein the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period of five weeks is in the range of 0.5 to 1.5 micrograms/kilogram BIW for one week, followed by 1.0 micrograms/kilogram BIW for four weeks and the amount of pegylated

20   interferon alfa-2b administered in the second treatment time period of forty-three weeks is in the range of 0.5 to 1.0 micrograms/kilogram per week on a weekly basis.

14.   The use of any preceding claim, wherein the pegylated interferon-

25   alfa administered is a pegylated interferon alfa-2b and wherein the induction dosing amount of pegylated interferon alfa-2b administered in first treatment time period is 1.5 micrograms/kilogram BIW for twelve weeks, and the amount of pegylated interferon alfa-2b administered in the second treatment time period is 1.5 micrograms/kilogram per week on a

30   weekly basis for thirty- six weeks.

15.   The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and the amount of

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pegylated interferon alfa-2a administered is from induction dosing amount of pegylated interferon alfa-2a administered is in the range of 20 to 250 micrograms BIW, preferably 90 to 180 micrograms BIW, for at least four weeks, and the amount of pegylated interferon alfa-2a administered in the

5   second treatment time period is in the range of 20 to 250 micrograms per week on a weekly basis(QW), 90 to 180 micrograms QW, for up to forty four weeks.

16.   The use of any preceding claim, wherein the pegylated interferon-
10   alfa administered is a pegylated interferon alfa-2a and wherein in first treatment time period, the induction dosing amount of pegylated interferon alfa-2a administered is in the range of 20 to 250 micrograms BIW , preferably 90 to 180 micrograms BIW, for four to twelve weeks, and the amount of pegylated interferon alfa-2a administered in the second

15   treatment time period is in the range of 20 to 250 micrograms per week on a weekly basis(QW), preferably 90 to 180 micrograms QW, for thirty six to forty four weeks.

17.   The use of any preceding claim, wherein the pegylated interferon-
20   alfa administered is a pegylated interferon alfa-2a and wherein in first treatment time period, the induction dosing amount of pegylated interferon alfa-2a administered is in the range of 20 to 250 micrograms BIW for one week, preferably 90 to 180 micrograms BIW, for one week, followed by 20 to 200 micrograms BIW, preferably 120 to 180 micrograms BIW, for four

25   weeks, and the amount of pegylated interferon alfa-2a administered in the second treatment time period administered is in the range of 20 to 250 micrograms per week on a weekly basis(QW), preferably 90 to 180 micrograms QW, for forty-three weeks.

30   18.   The use of any preceding claim, wherein the pegylated interferon-alfa administered is a pegylated interferon alfa-2a and wherein in first treatment time period, the induction dosing amount of pegylated interferon alfa-2a administered is in the range of 20 to 250 micrograms

BIW, preferably 90 to 180 micrograms BIW,for twelve weeks, and the amount of pegylated interferon alfa-2a administered in the second treatment time period is in the range of 20 to 250 micrograms per week on a weekly basis(QW), preferably 90 to 180 micrograms QW, for thirty-six

5   weeks.

19.   The use of any preceding claim wherein the patients having chronic hepatitis C are infected with multiple HCV genotypes including type 1.

10   20.   The use of any preceding claim wherein the patients having chronic hepatitis C are infected with HCV genotype 2 and/or 3.

21.   The use of any preceding claim wherein the patient is a treatment naïve patient.

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22.   The use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a method comprising administering an effective amount of ribavirin in

20   association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (1) a first treatment time period of about at least about four weeks, wherein about 400-1200 mg per day, preferably about 800-1200 mg per day, of ribavirin and about 1.5

25   micrograms per kilogram of pegylated interferon-alfa-2b twice a week are administered, (2) a second treatment time period of about up to about forty-four weeks, wherein about 800-1200 mg per day of ribavirin and about 1.0 to 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week are administered.

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23.   The use of both ribavirin and pegylated interferon alpha for the manufacture of pharmaceutical compositions for treating a patient having chronic hepatits C infection to eradicate detectable HCV-RNA by a

method comprising administering an effective amount of ribavirin in association with an effective amount of pegylated interferon alpha characterised in that treating patients having chronic hepatitis C infections is effected in two treatment time periods: (1) a first treatment time period

5   of about at least about four up to about twelve weeks, wherein about 400-1200 mg per day, preferably about 800-1200 mg per day, of ribavirin and about 1.5 micrograms per kilogram of pegylated interferon-alfa-2b twice a week are administered, (2) a second treatment time period of about thirty-six up to about forty-four weeks, wherein about 800-1200 mg per day of

10   ribavirin and about 0.5 to 1.5 micrograms per kilogram, preferably about 1.0 to 1.5 micrograms per kilogram of pegylated interferon-alfa-2b once a week are administered.

24.   The use of claims 22 or 23, wherein the patients having chronic

15   hepatitis C infection are treatment naive patients having HCV genotype 1, 2 or 3.

25.   The use of claims 22 or 23,, wherein the induction dosing amount of pegylated interferon alfa-2b administered in secondt time period is 1.5

20   micrograms/kilogram